Do genotype-based changes in serum uric acid really affect blood pressure?

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To the Editor: Parsa *et al.*[1] used Mendelian randomization to test the causal association between serum uric acid (SUA) and blood pressure. They found that decreases in SUA concentration due to a missense single-nucleotide polymorphism in the *GLUT9* gene are directly associated with a lower level of blood pressure and concluded that SUA is causally associated with blood pressure. However, in the association analysis of SUA and blood pressure, only age and gender were adjusted. We are wondering whether the association between SUA and blood pressure remains significant upon further adjustment for other important covariates. Actually, a previous study has shown that the relationship between SUA and blood pressure was attenuated by up to 50% upon further adjustment for body mass index, waist–hip ratio, or body fat percent.[2] A recent meta-analysis has found a modest but significantly increased relative risk for incident hypertension in subjects with hyperuricemia, independent of traditional risk factors for hypertension.[3] However, adjusting for measures of insulin resistance could bias the effect estimates toward the null.[3] In our cross-sectional study including 4387 subjects randomly selected from a general population, SUA was significantly associated with systolic and diastolic blood pressures adjusting for gender and age, but the association was no longer significant after the further adjustment of body mass index and waist–hip ratio (Table 1). If the association between SUA and blood pressure is no longer significant after complete adjustment, then the causal association might not be proved even with the use of Mendelian randomization.

1. Parsa A, Brown E, Weir MR *et al.* Genotype-based changes in serum uric acid affect blood pressure. *Kidney Int* 2012; **81**: 502–507.
2. Lyngdoh T, Viswanathan B, Myers GJ *et al.* Impact of different adiposity measures on the relation between serum uric acid and blood pressure in young adults. *J Hum Hypertens*; e-pub ahead of print 22 September 2011.
3. Grayson PC, Kim SY, LaValley M *et al.* Hyperuricemia and incident hypertension: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)* 2011; **63**: 102–110.

The Authors Reply: We fully appreciate the concern raised by Zhang *et al.*[1] regarding the unadjusted association between serum uric acid (SUA) and blood pressure. Indeed, this was the reason for our performing the Mendelian randomization (MR) analysis.[2] MR is based on the tenet that genotype, which is randomly assigned during gamete formation and fixed, cannot be modified by any of the traditional risk factors (e.g., obesity and diabetes) that occur after conception and hence is not confounded by them.[3] It is critical for the reader to be cognizant of this premise and, moreover, recognize that our analysis looked at the environmentally unconfounded and unidirectional association between GLUT9 genotype and blood pressure, as opposed to the easily confoundable association between SUA and blood pressure.[2] Indeed, as proof of concept, we showed in Table 2 of our original article that SUA was strongly associated with glucose, renal function, and body mass index (P values of 2.5×10^{-8}, 1.4×10^{-14}, and 1.5×10^{-31}, respectively), while, as expected, the GLUT9 genotype was not associated with these factors.[2] Conferring with the premise of MR and the complete lack of association between GLUT9 genotype and glucose, obesity, dyslipidemia, and renal function, we suitably did not adjust for them in our analysis.[2] We refer Zhang *et al.*[1] and the interested reader to a few of many reviews, for further details on how the use of MR in the appropriate setting can allow for reliable causal inferences,[3,4] as in the case of SUA and blood pressure.

1. Zhang H, Zhu Z, Yao W *et al.* Do genotype-based changes in serum uric acid really affect blood pressure? *Kidney Int* 2012; **82**: 360.
2. Parsa A, Brown E, Weir MR *et al.* Genotype-based changes in serum uric acid affect blood pressure. *Kidney Int* 2012; **81**: 502–507.

Table 1 | Association between serum uric acid and blood pressure

	Systolic blood pressure (mm Hg)			Diastolic blood pressure (mm Hg)		
Serum uric acid (μmol/l)	*β*	s.e.	*P*	*β*	s.e.	*P*
Model 1	0.038	0.003	<0.0001	0.023	0.002	<0.0001
Model 2	0.026	0.003	<0.0001	0.016	0.002	<0.0001
Model 3	0.011	0.003	0.001	0.010	0.002	<0.0001
Model 4	−0.0002	0.003	0.95	0.0005	0.002	0.78
Model 5	−0.0014	0.004	0.69	−0.0015	0.002	0.43

Model 1 encompasses linear regression analysis of circulating uric acid and blood pressure; model 2, adjusted for age and sex; model 3, as model 2 plus antihypertensive medication and heart rate; model 4, as model 3 plus body mass index and waist-to-hip ratio; model 5, as model 4 plus triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and serum glucose.